【Grant-in-Aid for Scientific Research (S)】

Broad Section H

Title of Project : Elucidation of pathogenic immunological memory to understand the pathogenesis of intractable inflammatory diseases

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Research Project Number : 19H05650 Researcher Number : 50237468
Keyword : Immune systems, Airway inflammation, Allergy, Pathogenic immunological memory

【Purpose and Background of the Research】

The main purpose of our research is to investigate the mechanisms that control the differentiation of memory helper T cells and their induction of allergic airway inflammation (asthma). “Immunological memory” is a major issue in the field of immunology research. Recently, we identified two pathogenic memory Th2 cell populations (IL-5-high-producing and fibrosis-inducing memory Th2 cells) that are harmful to humans (Figure 1).

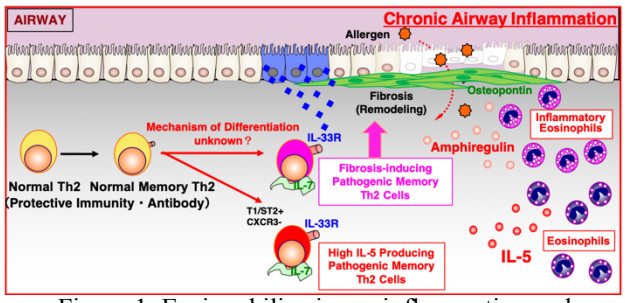

Figure 1: Eosinophilic airway inflammation and fibrosis induced by pathogenic memory Th2 cells

Based on these findings, we proposed a “pathogenic memory Th population disease induction model” in which pathogenic subpopulations induce and control the pathogenesis of various inflammatory diseases (Figure 2). We intend to explore the mechanisms underlying how pathogenic immunological memory T cells differentiate and are maintained in mouse models or human patients for a long time at the molecular and cellular levels.

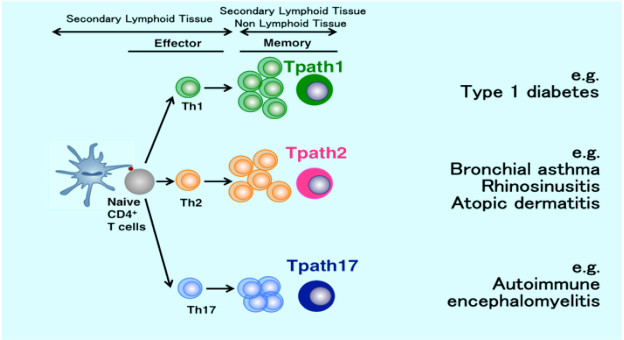

Figure 2: Pathogenic memory Th cells and inflammatory diseases

【Research Methods】

(1) To identify novel functional molecules regulating the pathogenesis and differentiation of "Pathogenic Memory Th2 (Tpath2) cells", we will conduct integrative analyses of Tpath2 cells using single-cell RNA-Seq, ChIP-Seq, or ATAC-Seq. We will also analyze the mechanism underlying the functional transformation and maintenance of Tpath2 cells regulated by Polycomb and Trithorax groups at the chromatin level. (2) In the spatio-temporal mapping of microenvironments responsible for the differentiation and maintenance of Tpath2 cells, we will examine immunohistological and pathological changes of inducible bronchus-associated lymphoid tissue (iBALT) and fibrosis of localized inflammation. (3) To promote research in support of a proof of concept, we will perform analyses using samples of human patients with chronic eosinophilic sinusitis, chronic hypersensitivity pneumonitis, eosinophilic esophagitis, and other diseases.

【Expected Research Achievements and Scientific Significance】

This research aims to clarify the nature of “pathogenic immunological memory”, both at the molecular and cellular levels, and to define the regulation of pathogenesis by immunological memory *in vivo*. These points of view are unique and scientifically significant. We will also focus on human immunology: we plan to analyze the inflamed tissues of several patients as well as human cells in almost all experiments. We additionally intend to examine the concepts derived from animal experiments to see if they can be applied to humans. Once we have determined how to control the number or function of immunological memory cells, this research may help contribute to the development of new treatment strategies for intractable inflammatory diseases.

【Publications Relevant to the Project】

- Morimoto Y, Nakayama T, et al., Amphiregulin-producing pathogenic memory T helper-2 cells instruct eosinophils to secrete Osteopontin and facilitate airway fibrosis. *Immunity* 49:134-150 (2018).
- Nakayama T, et al., Th2 Cells in Health and Disease. *Annu. Rev. Immunol.* 35:53-84 (2017).

【Term of Project】 FY2019-2023

【Budget Allocation】 155,400 Thousand Yen

【Homepage Address and Other Contact Information】

https://www.m.chiba-u.ac.jp/class/meneki/english/index.html